(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 May 2005 (19.05.2005)

PCT

(10) International Publication Number
WO 2005/045001 A3

(51) International Patent Classification[7]: C12P 21/04, C12N 5/00, 5/02, 5/06, 5/08, 5/10

(21) International Application Number: PCT/US2004/004681

(22) International Filing Date: 17 February 2004 (17.02.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/447,684 14 February 2003 (14.02.2003) US

(71) Applicant *(for all designated States except US)*: **THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY** [US/US]; 1705 El Camino Real, Palo Alto, CA 94306-1106 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HORI, Yuichi** [JP/JP]; 6-14-C505, Minatojima-nakamachi, Chuo-ku, Kobe 650-0046 (JP). **KIM, Seung** [US/US]; 817 Pine Hill Road, Stanford, CA 94305 (US).

(74) Agents: **VINCENT, Matthew, P.** et al.; Ropes & Gray LLP, One International Place, Boston, MA 02110-2624 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

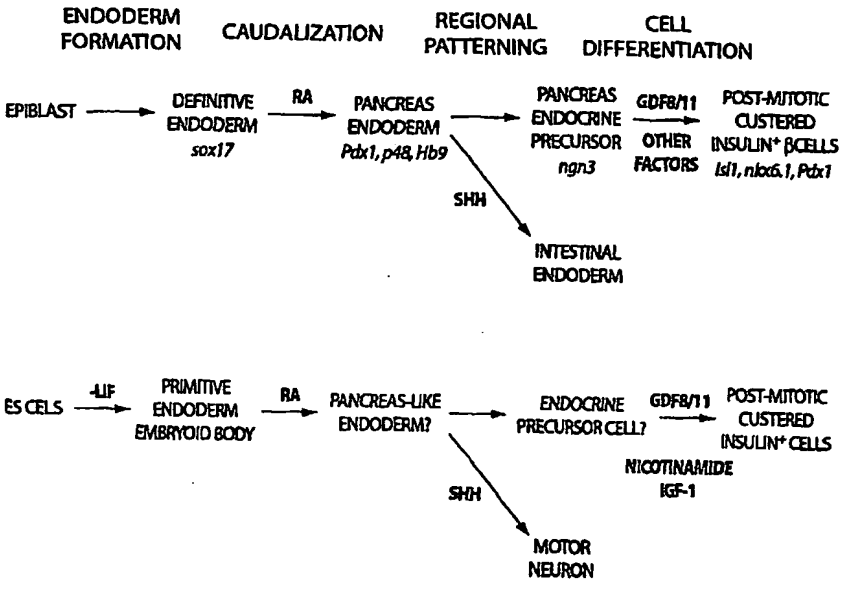
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
4 August 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INSULIN-PRODUCING CELLS DERIVED FROM STEM CELLS



(57) Abstract: The disclosure provides, among other things, insulin-producing cells derived from stem cells, such as human stem cells and neural stem cells. The disclosure discloses a relationship between caudalizing factors and the differentiation of insulin-producing cells.

WO 2005/045001 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/04681

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12P 21/04; C12N 5/00, 5/02, 5/06, 5/08, 5/10
US CL : 435/70.1, 325, 352, 363, 366, 368
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/70.1, 325, 352, 363, 366, 368

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZULEWSKI, H. ET AL. Multipotential Nestin-Postive Stem Cells Isolated From Adult Pancreatic Islets Differentiate Ex Vivo Into Pancreatic Endocrine, Exocrine, and Hepatic Phenotypes. March 2001, Vol. 50, No. 3, pages 521-533, see Figure 4.	1-9
A	LECHNER, A. ET AL. Nestin-Postive Progenitor Cells Derived from Adult Human Pancreatic Islets of Langerhans Contain Side Population (SP) Cells Defined by Expression of the ABCG2 (BCRP1) ATP-binding Cassette Transporter. Biochemical and Biophysical Research Communications 03 May 2002, Vol. 293, No. 2, pages 670-674, entire document.	1-9
A	BANI-YAGHOUB, M. ET AL. Insulin Acts as a Myogenic Differentiation Signal for Neural Stem Cells with Multilineage Differentiation Potential. Development September 2004, Vol. 131, No. 17, pages 4287-4298, entire document.	1-9
A	BURNS, C.J. ET AL. The in vitro differentation of rat neural stem cells into an insulin-expressing phenotype. Biochemical and Biophysical Research Communications 21 January 2005, Vol. 326, No. 3, pages 570-577, entire document.	1-9
A	CHOI, Y. ET AL. Adult Pancreas Generates Multipotent Stem Cells and Pancreatic and Nonpancreatic Progeny. Stem Cells 2004, Vol. 22, No. 6, pages 1070-1084, entire document	1-9

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
15 March 2005 (15.03.2005)

Date of mailing of the international search report
08 JUN 2005

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Christopher J. Nichols, Ph.D.
Valerie Bell-Harris for

Telephone No. (571) 272-1600

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/04681

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SEABERG, R. M. ET AL. Clonal Identification of Multipotent Precursors from Adult Mouse Pancreas that Generate Neural and Pancreatic Lineages. Nature Biotechnology September 2004, Vol. 22, No. 9, pages 1115-1124.	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/04681

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-9

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/04681

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-9, drawn to an insulin-producing cell.

Group 2, claim(s) 10-16, drawn to a method for making a cell composition comprising cells that are receptive to treatment with an islet cell differentiation factor.

Group 3, claim(s) 17-23, drawn to a method for making insulin-producing cells comprising culturing neural or neuroendocrine stem cells in at least two different media.

Group 4, claim(s) 24-25, drawn to a method for assessing a test agent.

Group 5, claim(s) 26, drawn to a therapeutic cell composition.

Group 6, claim(s) 27-30 and 45-53, drawn to a method of ameliorating a condition related to insufficient pancreatic function.

Group 7, claim(s) 31, drawn to a non-human animal.

Group 8, claim(s) 32-35, drawn to a method for testing the developmental potential of a cell of interest.

Group 9, claim(s) 36-38, drawn to a method for predicting the ability of an affinity reagent to bind to a pancreatic progenitor cell.

Group 10, claim(s) 39-44, drawn to a method for making human insulin producing cells.

According to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. The inventions listed as Groups 1-10 do not relate to a single general inventive concept because they lack the same or corresponding special technical feature. The technical feature of Group 1 is an insulin producing cell which is shown by ZULEWSKI et al. Multipotential Nestin-Positive Stem Cells Isolated From Adult Pancreatic Islets Differentiate Ex Vivo Into Pancreatic Endocrine, Exocrine, and Hepatic Phenotypes. Diabetes March 2001, Vol. 50, No. 3, pages 521-533. ZULEWSKI et al. teaches a nestin-positive insulin producing cell culture thus the special technical feature of claim 1 lacks novelty and does not make it a contribution over the prior art (see Figure 4).

Group 1 is drawn to the special technical feature of an insulin-producing cell, which is not required by any of the other groups.

Group 2 is drawn to the special technical feature of cells that are receptive to treatment with an islet cell differentiation factor, which is not required by any of the other groups.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/04681

Group 3 is drawn to the special technical feature of culturing neural or neuroendocrine stem cells in at least two different media, which is not required by any of the other groups.

Group 4 is drawn to the special technical feature of test agent, which is not required by any of the other groups.

Group 5 is drawn to the special technical feature of therapeutic cell composition, which is not required by any of the other groups.

Group 6 is drawn to the special technical feature of method of ameliorating a condition related to insufficient pancreatic function, which is not required by any of the other groups.

Group 7 is drawn to the special technical feature of a non-human animal, which is not required by any of the other groups.

Group 8 is drawn to the special technical feature of testing the developmental potential of a cell of interest, which is not required by any of the other groups.

Group 9 is drawn to the special technical feature of a method for predicting the ability of an affinity reagent, which is not required by any of the other groups.

Group 10 is drawn to the special technical feature of a method for making human insulin producing cells, which is not required by any of the other groups.

Continuation of B. FIELDS SEARCHED Item 3:
WEST (USPT, PGPUBS, US OCR, JPO, EPO, DERWENT); STN (BIOSCIENCE); NCBI (PUBMED)
neural, neuroendocrine, stem cell, insulin, pancreas, nestin, glucagon, somtatostatin, precursor cell, multipotent cell